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SULPHONAMIDES.

Classification.

Most of the sulphonamides have a full chemical name, an abbreviated chemical name, and various proprietary names. For example, the substance p-aminobenzenesulphonamide is given the abbreviated name of sulphanilamide and is also sold under such names as "Streptocide" and "Prontosil album". The use of trade names should not be encouraged by doctors, and full chemical names are not necessary in clinical discussions, so that the short chemical name is the one most freely used in medical literature and most likely to be adopted in the pharmacopœia.

The general term "sulphonamide" is applied to a whole group of drugs, of which the five most important members, at the present time, are sulphanilamide, sulphapyridine ("M & B 693"), sulphathiazole ("M & B 760"), sulphadiazine and succinylsulphathiazole. This list excludes several drugs of interest: "Prontosil rubrum", which was the first of the series to be used, but which is active only when broken down to sulphanilamide; sulphaguanidine, which is being replaced by succinylsulphathiazole; sulphacetamide ("Albucid"), which was once extensively used for gonorrhœa and staphylococcal infections, but which is very inferior to sulphathiazole; and several new drugs not yet fully tried—for example, sulphamethazine, an English drug closely related to the American product sulphadiazine.

Absorption.

Sulphanilamide is rapidly absorbed from the small intestine. If three grammes are taken by mouth, the blood level reaches a maximum in three hours, and absorption is complete in four hours. Sulphapyridine is absorbed more slowly and irregularly, but the absorption of sulphathiazole and sulphadiazine resembles that of sulphanilamide. After the fourth hour the amount of drug in the blood decreases rapidly, except in the case of sulphadiazine. All these facts determine the method of dosage. A large initial dose is given, and this is followed by smaller amounts at four-hourly intervals, or, in the case of sulphadiazine, at six-hourly intervals.

Succinylsulphathiazole is far different in its behaviour. Only about 3% is absorbed; the remainder stays in the intestine and this renders the drug an efficient intestinal antiseptic.

Distribution in the Body.

The sulphonamides diffuse readily into most body tissues and fluids. They pass freely into exudates and transudates. In the cerebro-spinal fluid all except sulphathiazole attain a concentration which is 50% to 65% of that in the blood. The corresponding figure for sulphathiazole is 20%.

Excretion.

The sulphonamides are excreted almost entirely in the urine, partly in a free, and partly in an acetylated, form. The latter, as well as being therapeutically inactive, is less soluble and more toxic than the free form. The acetylated fraction is greatest in the case of sulphapyridine, less for sulphathiazole, less still for sulphanilamide and least for sulphadiazine. This fraction increases if excretion is delayed.

Methods of Administration.

Oral administration is to be preferred for obtaining systemic effects, but may be impossible because of coma, nausea, delirium or a previous abdominal operation. Sulphanilamide can be injected intravenously as a 1% solution in saline, but the other compounds are so insoluble that they have to be given as 5% aqueous solutions of the sodium salts, which are very alkaline and irritant. There are certain objections to intravenous administration: the blood level falls rapidly, so that an effective blood concentration is not maintained for long; necrosis, abscess formation and ulceration follow if any of the alkaline drug is spilled into the areolar tissue around the vein; and, finally, the veins are sclerosed by repeated injections. Intramuscular injections are satisfactory, but care must be taken to avoid injecting solution into the subcutaneous tissues. Not more than three cubic centimetres should be given at a time, otherwise fluid is likely to come back along the needle track into the subcutaneous area. Concentrated solutions of the sodium salts (33·3%) should therefore be used. These are as alkaline as tenth normal caustic soda, so that good technique must be employed for the intramuscular injection: the injection is made deeply into the gluteal muscle at the junction of the upper and middle thirds of a line joining the anterior superior iliac spine to the ischial tuberosity; a bubble of air is trapped in the syringe and forced through after the solution.

The sulphonamides are being used more and more as local applications, especially in the prophylaxis of wound infection. The results are merely encouraging, and there is no warrant for relaxing the standards of surgical operative technique. The good surgeon is helped, but the poor surgeon may be hoodwinked, by the local use of these drugs. Thorough excision of wounds is necessary, because the drug will not penetrate necrotic tissue.

Some surgeons have claimed success in the local use of sulphonamides for established infection. Pus inactivates large quantities of the drug very readily, so that the treatment is not likely to be effective unless the pus can be cleared away. The difficulty of doing this completely, and the inability of sulphonamides to cope with large numbers of organisms, help to account for the poorer results in therapeutic as compared with prophylactic local application.

In selecting the drug to be used for local application the properties shown in Table I are important.[1]

Sulphanilamide has the advantage of being relatively soluble, so that it quickly reaches a high concentration, and readily diffuses into inaccessible parts of the wound. It persists as crystals for such a short time that it does not provoke a foreign body reaction. It is preferred for intraperitoneal use, where the danger of producing adhesions by foreign body reactions is an important hazard. It is also probably the most popular drug for surface wounds, but it has the disadvantages of being rapidly absorbed, and of being relatively ineffective against such common organisms as staphylococci and the gas

TABLE I.

Data Useful in Selecting Sulphonamides for Local Application.

Property.	Sulphonamide.			
	Sulphanilamide.	Sulphathiazole.	Sulphadiazine.	Sulphapyridine.
Solubility in serum at 37° C. in milligrammes *per centum*	1,600	184	124	61
Persistence as crystals in wound	6–24 hours	5 days	6 days	9 days
Excretion in twenty-four hours	50%	18%	?	7%
Diffusion time in wounds (time taken for a therapeutic amount to diffuse a given distance)	<2 hours	2–6 hours	6–24 hours	>24 hours

gangrene group. Some workers therefore recommend that one part of sulphadiazine should be used in conjunction with two or three parts of sulphanilamide, especially when the wound is to be dressed infrequently. Sulphathiazole would, of course, have to be considered as a rival to sulphadiazine; it is, in fact, superior to sulphadiazine in many respects, as Table I shows, and has been used fairly extensively; but, on the other hand, it is more toxic than sulphadiazine. Sulphapyridine is inferior to sulphadiazine and is not often used now. A foreign body reaction is provoked by sulphathiazole, sulphadiazine and sulphapyridine on account of the time the crystals persist in the wound.

Interest has been roused in the sterilization of sulphonamide crystals, by the occurrence of a case of tetanus, which may have been due to organisms present in the sulphonamide. An investigation of commercial sulphonamide crystals showed that they were rarely sterile, although they seemed to be satisfactory in practice. Some manufacturers have now begun to produce a sterile product. Sterilization can be effected by heating the dry crystals to 150° C. for two hours, but this temperature is rather close to the melting point of sulphanilamide (163° C.), although most of the other sulphonamides have higher melting points. One commercial firm uses hot air sterilization at 145° C. for four hours. Other suggestions for sterilization are to autoclave the powder, which normally contains 0·2% to 0·5% of water, in a tightly stoppered container, at ten pounds pressure for one hour, or to dissolve the drug temporarily in acetone and pass the solution through a Seitz filter. None of these methods is completely satisfactory as regards convenience, reliability of sterilization, and freedom from untoward destructive action.

The advantages of the local use of sulphonamide can be obtained without serious risk of toxic effects. The local toxic action of even a saturated solution of these drugs is not very great, but, possibly, direct damage may be done to exposed nerve trunks. A few cases have been reported in which so much sulphonamide was used that the absorbed drug had a general toxic action. This is not likely if the dose is restricted to 0·1 gramme per square inch of wound, with a maximum total of 10 grammes per day.

Dosage.

There are certain doses which may be taken as a standard guide and modified according to the progress of the patient and the level of free drug in the blood. The blood level aimed at in conditions other than meningitis is ten milligrammes per 100 cubic centimetres for sulphanilamide, and more than five milligrammes per 100 cubic centimetres in the case of sulphathiazole, sulphapyridine and sulphadiazine. In the treatment of meningitis the corresponding levels are 15, and 10 to 15, respectively. Although it is satisfying to have these estimations made, the facilities for carrying them out may not be available. Moreover, it is only in the case of sulphanilamide therapy that one gets a reasonably good correlation between therapeutic effect and concentration of drug in the blood.

For oral administration of sulphanilamide, three to five grammes are given initially, and thereafter 1·0 to 1·3 grammes every fourth hour, day and night, until the temperature has been normal for seventy-two hours and definite clinical evidence of improvement is seen. The amount given is then gradually reduced. Sulphapyridine and sulphathiazole have an initial dose of three to four grammes and a subsequent dose of one gramme. Sulphadiazine also has an initial dose of three to four grammes, but a subsequent dose of one gramme is given at six-hourly intervals. Succinylsulphathiazole is given at the rate of half a gramme per kilogram of body weight on the first day and at half this rate subsequently.

In the case of intravenous injections, sulphanilamide, sulphapyridine and sulphathiazole are given six-hourly, and sulphadiazine twelve-hourly. The initial dose in all cases is 0·06 gramme per kilogram of body weight and the subsequent dose half of this. As soon as the patient can take the drug by mouth, intravenous injections are discontinued.

Mode of Action.

In the last three years a theory of the mode of action of sulphonamides has been developed, and the general outline of it is now widely accepted. The theory is perhaps most useful as a means of giving a rational approach to the problem of finding new chemotherapeutic drugs; the old method, it has been said, was to delve into a lucky dip; the new is to construct a preparation according to a plan. The theory is also of interest to the clinician, however, since it raises certain practical points.

It is now well known that p-aminobenzoic acid inhibits the bacteriostatic and bactericidal actions of sulphonamides. It is also known that the same acid is necessary for the growth of certain organisms: some of them require it preformed and others probaby metabolize it themselves. When the chemical similarity between p-aminobenzoic acid and p-aminobenzenesulphonamide (sulphanilamide) is remembered, it is a reasonable theory that the sulphonamides injure bacteria by substrate competition—that is, they divert to themselves enzymes which normally carry out the essential metabolism of p-aminobenzoic acid. A working rule for one branch of experimental chemotherapy, therefore, is to elaborate substances which are so similar to p-aminobenzoic acid that they block its enzyme systems, but which are sufficiently different from it to be unable to produce its specific effect on bacterial growth. Other essential metabolites may be found, and other closely related substances will then be expected to act as chemotherapeutic drugs.

This theory raises the question of whether various sulphonamides can be specific for particular organisms. It is commonly believed that sulphathiazole is the best drug to use against staphylococci, but not against streptococci. Specificity, of course, cannot be explained on the theory that sulphonamides act only by competing with p-aminobenzoic acid. This problem has caused various workers to suggest that the thiazole group, for example, may have an affinity for staphylococci; but it has also led to the belief that specificity is not as marked as was formerly supposed. Sulphathiazole is the most active of the sulphonamides against staphylococci, but it is also the most active against the other susceptible organisms. Other sulphonamides replace sulphathiazole therapeutically only because they are less toxic, more soluble, better absorbed, or otherwise more convenient, and at the same time sufficiently potent against the organism concerned.

The action of pus in inhibiting sulphonamides is now well explained, since pus contains anti-sulphonamide substances, chiefly p-aminobenzoic acid, which are probably released from bacteria and from digested tissues. Procaine and related local anæsthetics can also inhibit sulphonamides because of the chemical similarity between the two groups of substances.

Choice of Sulphonamide.

At the present time, in Australia, sulphathiazole, sulphadiazine and succinylsulphathiazole are not readily obtainable; but, as the following account shows, this loss is not as great as it at first appears. A tabulation may be made showing various susceptible organisms and their reaction to the sulphonamides, as follows.[2] (a) In regard to streptococci, sulphadiazine is the most suitable drug, but

sulphanilamide is also very effective; sulphapyridine and sulphathiazole are active against streptococci, but are more expensive than sulphanilamide. (*b*) In regard to the pneumococcus, sulphanilamide is not effective, but sulphadiazine, sulphathiazole and sulphapyridine are; sulphadiazine is probably to be preferred because of its low toxicity. (*c*) In regard to the staphylococcus, sulphathiazole is the only sulphonamide which affects this organism readily, but large doses of sulphadiazine give some protection against it; no sulphonamide can sterilize localized collections of staphylococcal pus, such as are present in carbuncles and chronic osteomyelitis. (*d*) In regard to the meningococcus, sulphanilamide, sulphadiazine, sulphathiazole and sulphapyridine are all active against this organism. (*e*) In regard to the gonococcus, the drugs, arranged in descending order of their activity, are sulphathiazole, sulphadiazine, sulphapyridine and sulphanilamide. (*f*) In regard to *Clostridium welchii*, the results are not spectacular; sulphanilamide has little effect, but sulphathiazole, sulphapyridine and sulphadiazine are rather better; no sulphonamide affects *Clostridium œdematiens*, which was a frequent cause of gas gangrene in the Libyan battles. (*g*) In regard to *Bacillus influenzæ*, sulphathiazole, sulphadiazine, sulphapyridine and sulphanilamide all have some effect in influenzal meningitis, but the results are only fair. (*h*) In regard to urinary tract organisms, sulphathiazole is very good in pyelitis, and the results with sulphadiazine, sulphapyridine and sulphanilamide are also satisfactory. (*i*) In regard to *Bacillus dysenteriæ*, this is effectively combated by succinylsulphathiazole or sulphaguanidine; the latter gives an occasional severe reaction. (*j*) In regard to *Brucella abortus*, sulphadiazine is used, with fair results, to combat this, and sulphanilamide, sulphathiazole and sulphapyridine also probably have some effect on it. (*k*) In regard to virus infections, trachoma and *lymphogranuloma inguinale* have been shown to respond in some cases to sulphanilamide, sulphapyridine and sulphathiazole, and presumably to sulphadiazine. In choosing the most suitable sulphonamide in each case regard is paid to the fact that sulphadiazine is the least toxic and sulphanilamide the least expensive drug.

Toxic Actions.

The sulphonamides are administered so often that it is important to study even the more rare toxic effects that are caused by them. New drugs or drugs which are used occasionally may not reveal their toxic actions readily, and in the case of the sulphonamides we have had to learn afresh the old lesson that time, as well as faithful observation, is required to discover the undesirable side-actions of a drug. Sulphathiazole was introduced with the claim that it was less toxic than sulphapyridine. It causes less nausea and vomiting, admittedly, and so is perhaps less obtrusively toxic, but with the passage of time we have had to add to its toxic actions such fatal manifestations as anuria, acute hæmolytic anæmia, agranulocytosis and acute thrombocytopenic purpura. Similarly, sulphadiazine was said to be so soluble that renal complications from its use were unlikely, and the early cases of anuria caused by sulphadiazine were reported almost apologetically. Further experience has shown that sulphadiazine can also cause agranulocytosis; one can hardly hope that it will never cause acute hæmolytic anæmia.

The toxic actions due to the four chief sulphonamides are shown in Table II.

These reactions will now be discussed in turn.

Nausea and vomiting are a serious problem when one is using sulphapyridine, but are not very troublesome in the case of sulphadiazine. Various preparations such as nicotinic acid or sodium bicarbonate have been given with the sulphonamides in order to prevent nausea, but have not been successful. The best way to avoid this toxic effect is to inject a suitable preparation of the drug intramuscularly, but this is required only in a few intractable cases.

Cyanosis is due to the formation of sulphæmoglobin, methæmoglobin and coloured hæmoglobin-sulphonamide compounds, and has not, therefore, the dread significance of cyanosis due to oxygen lack. It occurs to a marked degree only when sulphanilamide is being used, and can be safely disregarded. Restrictions of sulphur-containing foods and of magnesium sulphate purges are not indicated.

Dizziness is an important complication in the case of those patients who drive automobiles, pilot aeroplanes or do any other work in which manipulative skill is necessary. Such patients should not be given ambulatory treatment with sulphonamides.

Drug fever occurs most commonly from the fifth to the ninth day, by which time the pyrexia due to the disease has usually subsided. The fever is often accompanied by headache and malaise. The drug should be discontinued whenever fever recurs after a normal temperature has been attained in the course of sulphonamide therapy. Abundant fluids should be given, with the idea of promoting elimination of the drug. The temperature usually returns to normal in twelve to seventy-two hours.

The drug rashes take on many forms, but can be divided into three main types on the basis of ætiology. In the first type the drug produces a photosensitivity, and the appearance of the actual rash is then dependent on exposure to light; only the parts so exposed are affected. In these cases excessive sunlight must be avoided, and, if this is done, the initial rash may be disregarded and administration of the drug continued. The second type of rash is a generalized eruption usually appearing at the eighth to the tenth day, allergic in type and often accompanied by a pyrexia of 100° to 101° F. It resembles serum sickness and is the most common of the three types. The generally accepted view is that in these cases one should continue to use the drug carefully for a further forty-eight hours, with the idea of desensitizing the patient. The patient is given a reduced dose and is kept under observation during this time. The third type of rash is due to retention of the drug, and is uncommon if administration is restricted to a seven-day period. It is a

TABLE II.
Showing Frequency with which Toxic Reactions are Caused by Different Sulphonamides.

Toxic Reaction.	Frequency of Occurrence.	Sulphonamide.			
		Sulphanilamide.	Sulphapyridine.	Sulphathiazole.	Sulphadiazine.
Nausea with or without vomiting	5%–60%	+++	++++	++	+
Cyanosis	Common	++++	+++	+	+
Dizziness	Common	+++	+++	+	+
Fever	2%–10%	++++	+++	+++	++
Rash	2%–10%	+++	+++	++++	++
Acute hæmolytic anæmia	0%–1·5%	+	+	+	–
Other anæmias	0%–4%	++++	+++	+	+
Neutropenia	0·1%–2%	+	+	+	+
Agranulocytosis	0%–0·3%	+	+	+	+
Acute thrombocytopenic purpura	Rare	+	+	+	+
Hæmaturia	0%–10%	–	+++	+++	++
Anuria	0%–1%	–	+++	+++	++
Psychosis	0·5%–4%	+	++	++	++
Neuritis	Rare	+	+	+	–
Hepatitis	0%–0·5%	++	+	+	–
Conjunctivitis	0%–4%	–	–	+++	–
Acidosis	0%–2%	++	–	–	–

serious toxic effect, and may progress to exfoliative dermatitis. When it occurs, therefore, the drug should be discontinued. Since the excessive accumulation of drug in the blood usually implies that excretion has been inadequate, a simple test has been devised by Werner to detect the presence of significant amounts of sulphonamide in the urine. One cubic centimetre of urine is diluted ten times, and to it are added a few drops of 3% p-dimethylaminobenzaldehyde in 7% aqueous solution of sulphuric acid. A yellow colour is given if significant amounts of sulphonamide are present.

Acute hæmolytic anæmia ranks with anuria and agranulocytosis as a possible cause of death from sulphonamide therapy. This anæmia develops as the result of an idiosyncrasy, and is therefore not dependent on the giving of a large dose of drug. One fatal case reported was caused by an amount of less than five grammes. The condition usually occurs suddenly on the second to the sixth day, and in twelve hours as much as one-third to two-thirds of the patient's blood may be hæmolysed. Deep jaundice develops in a few hours; the temperature rises and the white cells may undergo such an increase as to give a leuchæmoid blood picture. The drug should be stopped, fluids given freely, the urine made alkaline and blood transfusion given.

Much more common than acute hæmolytic anæmia, however, is an anæmia of a mild and slowly developing hæmolytic type. The hæmoglobin content may drop 20% in the first ten days of treatment. These anæmias generally disappear when the drug is discontinued, and are therefore important only in chronic diseases such as osteomyelitis, in which the drug may have to be given for long periods. They are combated by the administration of iron or, if necessary, by blood transfusion. A few of the slowly developing anæmias are probably aplastic in type.

Neutropenia may occur early in the course of treatment, but agranulocytosis is unusual before the twelfth day after the beginning of the course of sulphonamide. It is now known that these complications can be produced by sulphathiazole and sulphapyridine. In order to detect these toxic actions, white blood cell counts should be made regularly after the twelfth day of treatment. If a leucopenia supervenes, the drug should be withheld and fluid given freely.

Acute thrombocytopenic purpura is now known to be caused by any of the four chief sulphonamides. The treatment is to stop further doses of the drug and to try to eliminate that which has already been given.

Hæmaturia, in an amount detectable only by examination with the microscope, has an incidence as high as 10% in the case of sulphapyridine and sulphathiazole. The renal complications of sulphonamide therapy are very important, since they are the commonest of the potentially serious toxic actions. The mildest form is the microscopic hæmaturia referred to above. It may be accompanied by occasional pain in the lumbar region. The frequency with which this minor hæmaturia is reported depends on the thoroughness with which it is sought.

In some cases the hæmaturia is gross, and the pain is severe and more or less constant. This condition may clear up if the drug is withheld. The most serious injury is anuria. This may occur suddenly or be heralded by a period of oliguria. There is almost always some hæmaturia preceding the anuria.

The pathological changes are produced by the precipitation in the urinary tract of the drug or its less soluble acetylated derivative. On account of the relatively high solubility of sulphanilamide and acetylsulphanilamide, this complication is either rare or non-existent after sulphanilamide therapy, but it is an important danger during the use of sulphapyridine, sulphathiazole and even sulphadiazine. Some people seem to have a special tendency to form an abnormally large amount of the acetylated form of the drug. Blood cells and amorphous material tend to become associated with the precipitated crystals, and form an obstruction in one or both of the urinary tracts. Above the obstruction characteristic changes occur. The ureters and pelves become dilated and thinned and the kidneys enlarged and œdematous. The stasis encourages infection, and ureteritis, periureteritis and pyelitis occur. A large mass of crystalline deposit, blood and fibrin collects in the pelvis. The changes extend further back in the renal system; the tubules become dilated and degenerated and the glomerular space may be increased.

An important feature is that the obstruction is usually in the pelvis or ureter rather than in the renal parenchyma, so that ureteric catheterization and lavage is a rational and successful method of treatment. Whenever the prodromal signs of oliguria or hæmaturia appear, alkalis are usually given, but it is doubtful whether the urine can be made sufficiently alkaline to affect the solubility of the drug significantly. In all patients receiving sulphonamide therapy the fluid intake is kept up to three litres a day in an attempt to maintain a urinary output of 1,000 to 1,500 cubic centimetres. If, in spite of these measures, anuria occurs, or oliguria persists for twenty-four hours, cystoscopy and ureteric catheterization are carried out under local anæsthesia. The catheters are inserted up the ureters in turn, and if obstruction is encountered the pelvis and ureter are washed out with sterile water or saline solution which has been heated to 37° C. so as to facilitate solution of the crystals. A small amount of blood-stained urine comes away at first, but after half an hour or more the urine becomes clear and drips rapidly from the catheter. The catheter should be left indwelling for twenty-four to forty-eight hours and a retrograde pyelogram made prior to its withdrawal.

This method of treatment has proved very successful, but it should rarely be required if careful attention is paid to the urinary output. If vomiting occurs there is an increased likelihood of low renal excretion, and the fluid intake must be carefully maintained even if intravenous administration is necessary. It must be noted, however, that once anuria is established, the further administration of fluid accentuates the hydronephrosis, and may cause pulmonary œdema.

Mental depression is often a marked and worrying feature of sulphonamide therapy, and in a small percentage of cases a toxic psychosis occurs. Neuritis of either a peripheral or a central type may occur. Hepatitis is another complication, so that hæmolytic anæmia is not the only cause of jaundice during sulphonamide therapy. The hepatitis may be associated with exfoliative dermatitis. Conjunctivitis has been reported only from sulphathiazole therapy. Acidosis is probably due to the inactivation of carbonic anhydrase, and has been reported only in the case of sulphanilamide therapy. All of these complications clear up readily if the drug is withdrawn.

It is necessary to take certain general precautions against the toxic effects of sulphonamides. The patients should be seen once a day and questioned regarding headache and malaise, which are often the earliest toxic symptoms. An examination should be made for jaundice, pallor and rash, and the temperature chart should be inspected. The urinary output should be checked, and the urine examined microscopically for red blood cells. The presence of hæmaturia detectable by the microscope is a warning to be careful rather than a contraindication to the continuance of sulphonamide; crystalluria has the same significance. After the twelfth day of treatment neutrophile cell counts should be made once every two days. Hæmoglobin estimation should be made once a week. These are the minimum hæmatological investigations that it is desirable to make. The level of the sulphonamide in the blood should be measured after twenty-four hours of therapy and from time to time subsequently.

A person who has once had a toxic reaction to a sulphonamide drug may show an even more serious reaction if given any sulphonamide on a subsequent occasion. Before the second course is given, therefore, a small dose of 0·1 to 0·3 gramme should be tried, and the person should be kept under observation for twelve hours.

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